

University of Groningen

Right Heart Dysfunction in Heart Failure with Preserved Ejection Fraction

Gorter, Thomas M; van Melle, Joost P; Rienstra, Michiel; Borlaug, Barry A; Hummel, Yoran M; Van Gelder, Isabelle C; Hoendermis, Elke S; Voors, Adriaan A; Van Veldhuisen, Dirk J; Lam, Carolyn S P

Published in:
JOURNAL OF CARDIAC FAILURE

DOI:
[10.1016/j.cardfail.2017.11.005](https://doi.org/10.1016/j.cardfail.2017.11.005)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2018

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Gorter, T. M., van Melle, J. P., Rienstra, M., Borlaug, B. A., Hummel, Y. M., Van Gelder, I. C., Hoendermis, E. S., Voors, A. A., Van Veldhuisen, D. J., & Lam, C. S. P. (2018). Right Heart Dysfunction in Heart Failure with Preserved Ejection Fraction: the Impact of Atrial Fibrillation. *JOURNAL OF CARDIAC FAILURE*, 24(3), 177-185. <https://doi.org/10.1016/j.cardfail.2017.11.005>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Clinical Investigation

Right Heart Dysfunction in Heart Failure With Preserved Ejection Fraction: The Impact of Atrial Fibrillation

THOMAS M. GORTER, MD,¹ JOOST P. VAN MELLE, MD, PhD,¹ MICHIEL RIENSTRA, MD, PhD,¹ BARRY A. BORLAUG, MD,² YORAN M. HUMMEL, PhD,¹ ISABELLE C. VAN GELDER, MD PhD,¹ ELKE S. HOENDERMIS, MD, PhD,¹ ADRIAAN A. VOORS, MD, PhD,¹ DIRK J. VAN VELDHUISEN, MD PhD,¹ AND CAROLYN S.P. LAM, MD, PhD^{1,3}

Groningen, The Netherlands; Rochester, Minnesota; and Singapore

ABSTRACT

Background: Right ventricular (RV) dysfunction and atrial fibrillation (AF) frequently coexist in heart failure with preserved ejection fraction (HFpEF). The mechanisms underlying the association between AF and RV dysfunction are incompletely understood.

Methods and Results: We identified 102 patients. RV function was assessed with the use of multiple echocardiographic parameters, and dysfunction was present if ≥ 2 parameters were below the recommended cutoffs. RV function, right atrial (RA) reservoir strain, and RA emptying fraction were compared between AF and sinus rhythm. We included 91 patients with sufficient echocardiographic quality: 45 (50%) had no history of AF, 14 (15%) had earlier AF while in sinus rhythm, and 32 (35%) had current AF. The prevalence of RV dysfunction varied across subgroups (never AF, earlier AF, and current AF: 20%, 43% and 63%, respectively; $P = .001$). AF was associated with RV dysfunction (odds ratio [OR] 4.70 [95% confidence interval [CI] 1.82–12.1]; $P = .001$) independently from pulmonary pressures. In patients in sinus rhythm with earlier AF, RA emptying fraction was lower compared with patients without AF history (41 vs 60%; $P = .002$). Earlier AF was also associated with reduced RA reservoir strain (OR 4.57 [95% CI 1.05–19.9]; $P = .04$) independently from RV end-diastolic pressure.

Conclusions: Atrial fibrillation is strongly related to reduced RV and RA function in HFpEF independently from pulmonary pressures. (*J Cardiac Fail* 2018;24:177–185)

Key Words: HFpEF, Right ventricular dysfunction, Atrial fibrillation.

From the ¹Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; ²Division of Cardiovascular Diseases, Department of Medicine, Mayo Clinic, Rochester, Minnesota and ³Department of Cardiology, National Heart Center Singapore, Singapore Duke-NUS Graduate Medical School, Singapore.

Manuscript received May 12, 2017; revised manuscript received October 22, 2017; revised manuscript accepted November 22, 2017.

Reprint requests: Thomas M. Gorter, MD, Department of Cardiology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, PO Box 30.001, 9700 RB Groningen, The Netherlands. Tel: + 31 0503615995; Fax: + 31 0503611347. E-mail: tm.gorter@umcg.nl.

Conflict of interest: Dr Lam is supported by the Rosalind Franklin Fellowship. Dr Lam has received research support from Boston Scientific, Bayer, Thermofisher, Medtronic, Vifor, and Pharma outside of the submitted work, and has consulted for Bayer, Novartis, Takeda, Merck, AstraZeneca, Janssen Research and Development, Menarini, Boehringer Ingelheim, and Abbott Diagnostics outside of the submitted work. All other authors report no conflict of interest regarding the present work.

1071-9164/\$ - see front matter

© 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<https://doi.org/10.1016/j.cardfail.2017.11.005>

Right ventricular (RV) dysfunction and atrial fibrillation (AF) are common in patients with heart failure with preserved ejection fraction (HFpEF); they often coexist and are independently associated with a poor prognosis.^{1–3} Recent studies have indicated a potential relationship between AF and RV dysfunction in HFpEF.^{4–9} For example, the prevalence of AF in patients without RV dysfunction ranges from 31% to 53%, compared with 65%–73% prevalence of AF in HFpEF patients with RV dysfunction.^{4,5,7} Although these patients with RV dysfunction also had higher pulmonary pressures, the association between AF and RV dysfunction in HFpEF appeared to be unrelated to pulmonary pressures.^{4,9} Whether these patients with higher prevalence of both RV dysfunction and AF represent the “sicker” HFpEF patient is unknown. Possible load-independent factors associated with RV dysfunction in the setting of AF in HFpEF are incompletely understood, and studies with the primary aim to

investigate these associations have not been carried out. Furthermore, although left atrial (LA) remodeling in patients with HFpEF and AF is extensively investigated,¹⁰ the association with right atrial (RA) remodeling has so far not been studied and compared to simultaneous criterion-gold standard invasive hemodynamics in HFpEF-AF. We therefore aimed in the present study to compare RV and RA function in AF versus sinus rhythm among patients with HFpEF undergoing simultaneous right heart catheterization and echocardiography. We hypothesized that RA function is simultaneously impaired in HFpEF-AF and further contributes to RV dysfunction, independently from RV afterload.

Methods

The study population of this observational cohort study was recently described⁸ and consisted of 102 symptomatic HFpEF patients with New York Heart Association (NYHA) functional class \geq II and left ventricular ejection fraction (LVEF) \geq 45%, who had echocardiographic signs of elevated right-side pressures and therefore underwent routine left- and right-side heart catheterization for the evaluation of pulmonary hypertension. Patients without a simultaneous echocardiographic assessment were excluded. Patients were also excluded if RV systolic function could not be measured reliably with the use of \geq 2 recommended echocardiographic indices for RV systolic function (see further details below).

Baseline demographic and clinical characteristics, as well as heart rate during the assessment and atrial fibrillation/flutter history, were obtained. Patients also underwent a physical examination and a laboratory test, including N-terminal pro-B-type natriuretic peptide (NT-proBNP). Patients were divided into 3 subgroups: patients in sinus rhythm and without a history of AF (never AF), patients in sinus rhythm during the assessment but with an earlier diagnosis of AF (earlier AF) and patients who were in AF during the assessment (current AF).

Right Heart Catheterization Protocol

All patients underwent a right heart catheterization in fasting state and in supine position as previously described in detail.¹¹ The right heart catheterization was performed by a single experienced interventional cardiologist (ESH). A 7-F thermolubion balloon-tipped catheter was inserted through the femoral vein and advanced into the right atrium and right ventricle. The catheter was subsequently positioned in the pulmonary artery and wedge position. RA pressure, RV end-diastolic pressure (RVEDP), pulmonary artery pressure (PAP), and pulmonary capillary wedge pressure (PCWP) were obtained at end-expiration. Arteriovenous oxygen difference ($A-VO_2$ diff) was determined as the difference between directly measured arterial and mixed venous O_2 contents from blood sampling. Cardiac output (CO) was calculated by means of the Fick equation with the use of estimated O_2 consumption ($CO = VO_2/A-VO_2$ diff) and indexed for body surface area

to calculate cardiac index (CI). Pulmonary vascular resistance (PVR) was calculated as mean $(PAP - PCWP)/CO$.

Echocardiographic Protocol

Echocardiographic images were acquired simultaneously with the right heart catheterization by a single experienced ultrasound technician (YMH) with the use of a Vivid S6 system (General Electric, Horton, Norway) with a 2.5- to 3.5-MHz probe. Images were digitally stored for offline analyses. Analyses were independently performed by 2 experienced investigators (TMG and YMH) with the use of GE EchoPAC version BT12. All measurements were performed in duplicate on 2 time points, and the average values were calculated. For patients in AF, measurements were averaged from the available heart beats (3–4 cycles).

RV-focused apical 4-chamber views were obtained and RV dysfunction assessed by means of tricuspid annular plane systolic excursion (TAPSE), systolic annular tissue velocity of the lateral tricuspid annulus (RV S'), RV fractional area change (FAC), and RV free wall longitudinal strain (FWLS) according to previous recommendations.¹² RV dysfunction was considered present if \geq 2 of the measures of RV function were below the lower limit of normal (ie, TAPSE $<$ 17 mm, RV S' $<$ 9.5 cm/s, RV FAC $<$ 35%, and RV FWLS $>$ -20%).¹² Right ventricular myocardial performance index (RV Tei-index) was calculated by means of the tissue Doppler method (ie, isovolumetric time – isovolumetric relaxation time, divided by total RV ejection time), where larger values indicate poorer RV myocardial performance.¹² Right ventricular–vascular coupling was assessed by calculating the ratio of TAPSE to simultaneously derived invasive systolic PAP (ie, TAPSE/SPAP).¹³

Furthermore, RA maximum (end-systolic) and minimum (end-diastolic) volumes were calculated by summation of the discs in the apical 4-chamber view. Total RA emptying fraction was calculated as maximum volume – minimum volume, divided by maximum volume (Fig. 1A). With the use of 2-dimensional echocardiographic speckle tracking, RA endocardial contours were traced and RA reservoir strain subsequently measured (Fig. 1B). There are no established cutoff values for reduced RA emptying fraction and RA reservoir strain. Therefore, RA emptying fraction and reservoir strain were dichotomized on the basis of the median value, and reduced emptying fraction and reservoir strain were defined as the group below the median.

In addition, RA compliance was calculated as follows: RA stroke volume (ie, maximum – minimum volume) divided by RA pulse pressure (RA maximum – minimum pressure), obtained from the invasive RA pressure waves.¹⁴ RA compliance was expressed as mL/mm Hg.

Statistical Analyses

Data are summarized as mean \pm SD, median (interquartile range [IQR]) or n (%). analysis of variance was used to test between-group equality of the means of continuous variables. The Welch F test was used when the assumption

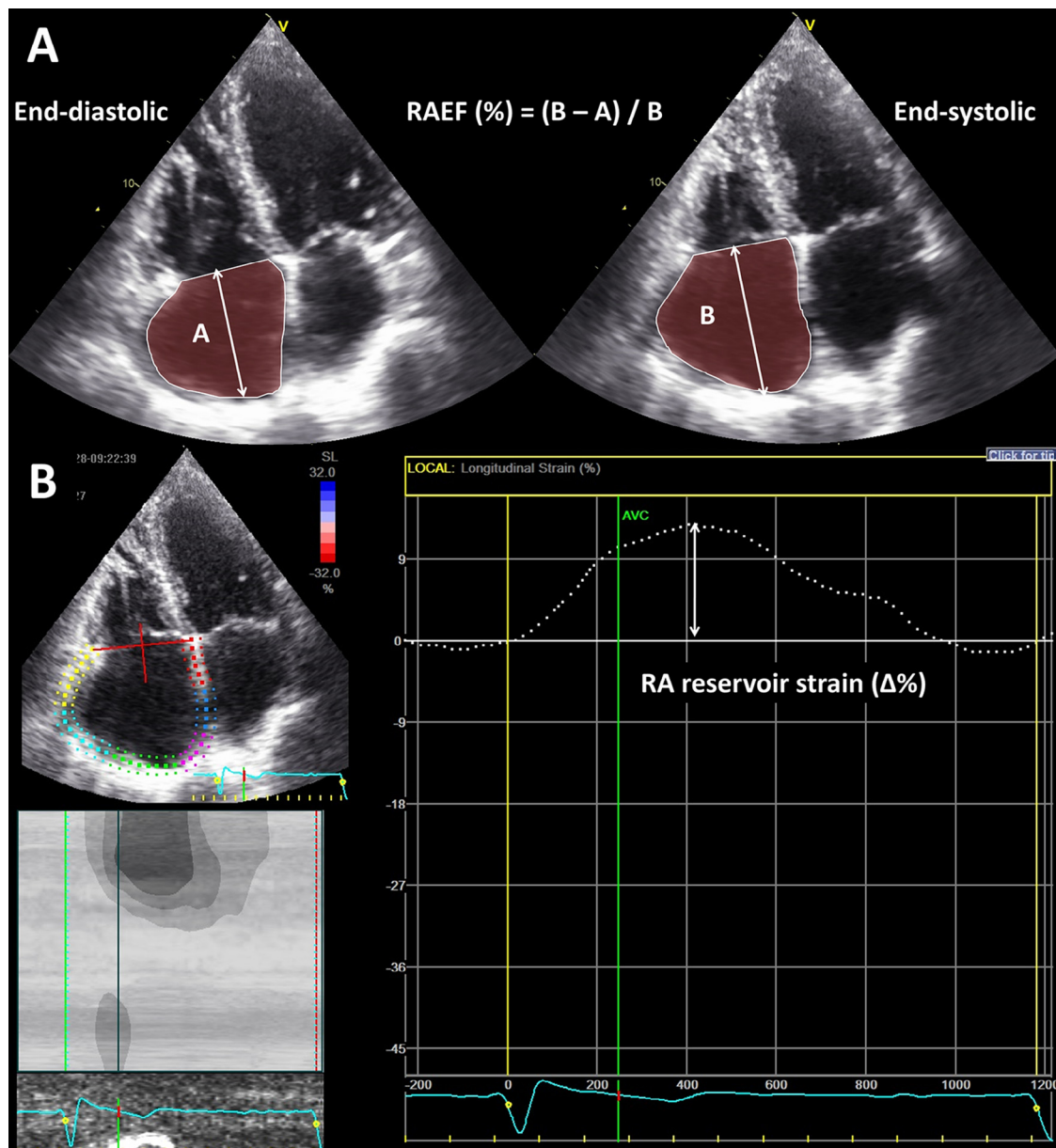


Fig. 1. Echocardiographic methods for the assessment of right atrial (RA) function. (A) Assessment of RA emptying fraction (RAEF) with the use of the area-length method in the apical 4-chamber view, and (B) assessment of RA reservoir strain with the use of echocardiographic 2-dimensional speckle tracking strain.

of homogeneity of variances was violated. In addition, multiple comparisons between subgroups were performed with Bonferroni correction. Chi-square tests and Fisher exact tests were used to test for differences in distributions of categorical variables. Associations with the presence of RV and RA dysfunction were conducted with the use of binary logistic regression. Unadjusted and adjusted odds ratios (ORs) with their 95% confidence intervals (CIs) were estimated. For continuous variables, ORs are presented per SD change to facilitate comparisons between ORs for different variables. The minimum number of events per adjustment variable in the logistic regression analysis was set at 10, based on previous recommendations.^{15,16} Statistical significance was considered to be achieved with P value $< .05$. All statistical

analyses were performed with the use of SPSS (version 22, 2013).

Results

Four patients were excluded from the identified study sample because they did not undergo simultaneous echocardiography. In 7 patients, RV systolic function could not be assessed reliably with ≥ 2 echocardiographic parameters, and those patients were excluded as well. Thus in total, 91 HFpEF patients were included in the present study.

Of these, 45 patients (49.5%) had no history of AF, 14 (15.4%) had earlier AF and were currently in sinus rhythm,

Table 1. Baseline Characteristics

Characteristic	Never AF (n = 45)	Earlier AF (n = 14)	Current AF (n = 32)	P Value
Age (y)	73 ± 8	76 ± 5	75 ± 11	.49
Male sex	11 (24%)	7 (50%)	10 (31%)	.19
Body mass index (kg/m ²)	28.3 ± 5.6	26.2 ± 2.8	29.1 ± 6.7	.33
New York Heart Association functional class II/III	58% / 42%	43% / 57%	19% / 81%*	.003‡
Hypertension	31 (69%)	9 (64%)	20 (63%)	.84
Coronary artery disease	15 (33%)	6 (43%)	11 (34%)	.80
Pacemaker	3 (7%)	4 (29%)	5 (16%)	.09
Chronic obstructive pulmonary disease	8 (18%)	1 (7%)	5 (16%)	.63
Right heart catheterization				
Heart rate (beats/min)	71 ± 11	68 ± 11	74 ± 15	.35
LV end-diastolic pressure (mm Hg)	17 ± 7	16 ± 6	18 ± 3	.75
Pulmonary capillary wedge pressure (mm Hg)	16 ± 7	17 ± 6	20 ± 4*	.01‡
Mean pulmonary artery pressure (mm Hg)	29 ± 10	29 ± 11	34 ± 7*	.03‡
RV end-diastolic pressure (mm Hg)	8 ± 4.0	8 ± 4.0	11 ± 4.0 *	.008*
Mean right atrial pressure (mm Hg)	7 ± 4	7 ± 4	11 ± 5*†	<.001‡
Cardiac index (l/min/m ²)	3.0 ± 0.6	3.3 ± 0.8	2.8 ± 0.8†	.04‡
Pulmonary vascular resistance (WU)	2.5 ± 2.1	2.3 ± 1.9	3.0 ± 1.3	.40
Echocardiography				
LV ejection fraction (%)	57 ± 5	58 ± 4	56 ± 5	.38
LV mass index (kg/m ²)	93 ± 36	93 ± 23	98 ± 24	.79
LV E/e'	12.9 ± 4.5	19.7 ± 11.7*	14.6 ± 7.2	.01‡
Septal wall e' (cm/s)	6.5 ± 2.0	4.9 ± 1.4	8.0 ± 3.2*†	.001‡
Lateral wall e' (cm/s)	8.2 ± 2.9	7.5 ± 2.4	11.0 ± 4.2*†	.001‡
Deceleration time (ms)	204 ± 51	222 ± 70	179 ± 53	.04‡
LA volume index (mL/m ²)	40 ± 12	47 ± 20	57 ± 17*	<.001‡
LA reservoir strain (%)	17.6 ± 7.2	13.0 ± 5.2	6.3 ± 2.5*	<.001‡
RV dysfunction	9 (20%)	6 (43%)	20 (63%)*	.001‡
≥ moderate tricuspid regurgitation	11 (24%)	5 (36%)	12 (38%)	.43
Medication				
Beta-blockers	37 (82%)	10 (71%)	27 (84%)	.57
Sotalol	0	2 (14%)	1 (3%)	.03‡
Calcium channel blocker	2 (4%)	1 (7%)	2 (6%)	.90
Amiodarone	0	0	2 (6%)	.15
Digitalis	1 (2%)	0	7 (22%)*	.005‡
Loop diuretics	34 (76%)	10 (71%)	27 (84%)	.53
Laboratory test				
NT-proBNP (ng/L)	481 (277–955)	1265 (485–2335)	1656 (1090–2567)*	.05

Data are reported as mean ± SD, median (interquartile range), and n (%). Subgroups: 1) no history of atrial fibrillation (ie, Never AF); 2) earlier atrial fibrillation and in sinus rhythm during the assessment (ie, Earlier AF); and 3) atrial fibrillation during the assessment (ie, Current AF). AF, atrial fibrillation; LA, left atrial; LV, left ventricular; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RV, right ventricular.

**P* < .05 vs Never AF group (with Bonferroni correction).

†*P* < .05 vs Prior AF group (with Bonferroni correction).

‡*P* < .05.

and 32 (35.2%) were currently in AF. Of the 14 patients with earlier AF, 7 (7.7%) had paroxysmal AF, 5 (5.5%) persistent AF, and 2 (2.2%) atrial flutter.

Patients with current AF had a median duration from 1st diagnosis of 7.5 (IQR 3.2–11.1) years, and for patients with earlier AF this interval from 1st diagnosis to baseline assessment was 2.0 (IQR 0.6–4.0) years. [Table 1](#) summarizes the baseline characteristics of the study population according to the 3 subgroups. Patients in AF were more symptomatic and had higher PCWP and PAP than patients who were in sinus rhythm.

Right Ventricular Function in Atrial Fibrillation Versus Sinus Rhythm

A total of 35 patients (38.5%) had RV dysfunction. As presented in [Table 1](#), the prevalence of RV dysfunction varied

significantly across the 3 subgroups (never AF, earlier AF, and current AF: 20%, 43%, and 63%, respectively; *P* = .001).

[Figure 2](#) illustrates the association between AF and echocardiographic parameters that reflect RV function. All measures of RV function were significantly lower in patients with current AF compared with patients without any history of AF. Patients with current AF also had higher RV Tei-index and lower TAPSE/SPAP ratio. Furthermore, there was a significant difference observed for all RV parameters across the 3 subgroups, but there were no statistical significant differences in RV parameters between the 2 subgroups in sinus rhythm (ie, never AF vs earlier AF).

[Table 2](#) details the logistic regression model for the association with RV dysfunction in HFpEF. AF, male sex, permanent pacing, and reduced LVEF remained associated with RV dysfunction after adjustment for mean PAP.

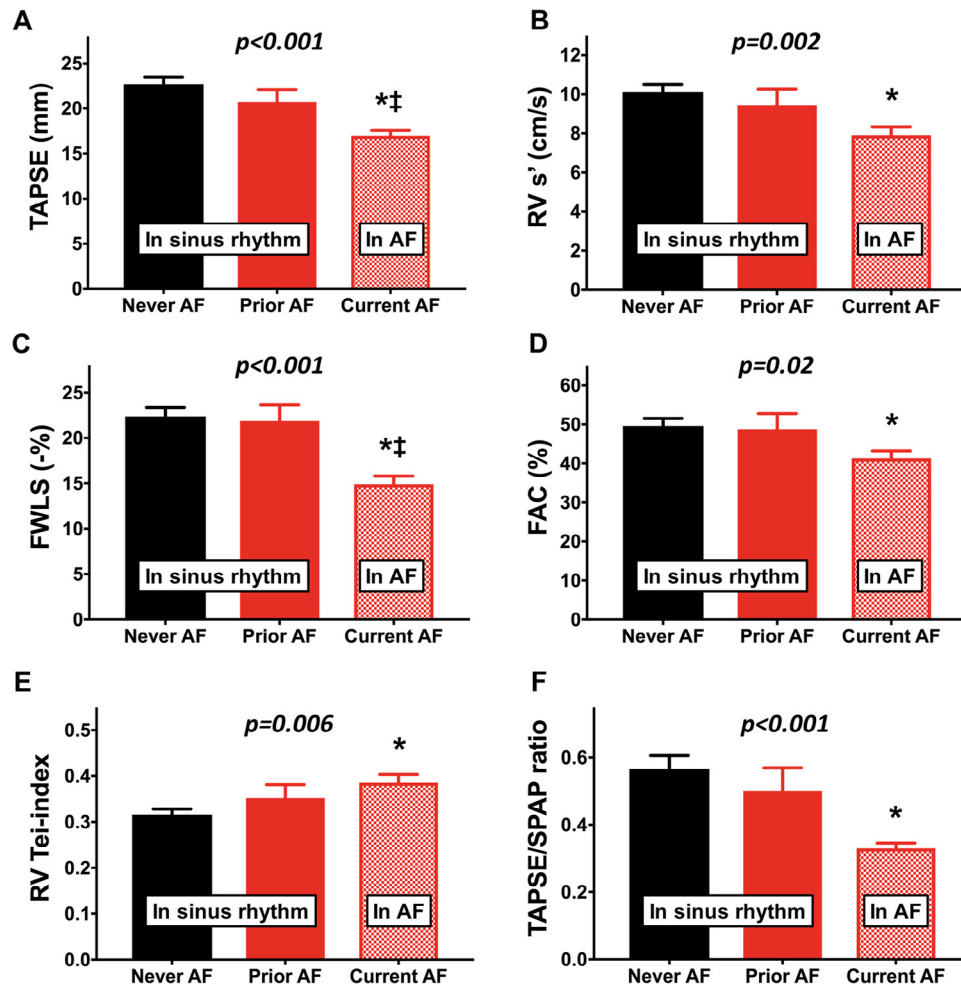


Fig. 2. Association between atrial fibrillation (AF) and right ventricular (RV) function. FAC, fractional area change; FWLS, free wall longitudinal strain; RV S' systolic annular tissue velocity of the lateral tricuspid annulus; RV Tei-index, right ventricular myocardial performance index; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion. * $P < .05$ vs Never AF group (with Bonferroni correction). † $P < .05$ vs Prior AF group (with Bonferroni correction). Error bars indicate SEM.

Table 2. Correlates of Right Ventricular Dysfunction

Variable	Univariable Model		PAP-Adjusted Model*	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Male sex	3.09 (1.23–7.76)	.02†	2.76 (1.07–7.11)	.04†
Any diagnosis of AF vs Never AF	5.20 (2.04–13.2)	.001†	4.70 (1.82–12.1)	.001†
Earlier AF vs Never AF	3.00 (0.83–10.9)	.09	3.11 (0.83–11.6)	.09
AF rhythm vs sinus rhythm	4.89 (1.94–12.3)	.001†	4.18 (1.62–10.8)	.003†
Coronary artery disease	2.47 (0.78–7.86)	.1	2.09 (0.84–5.16)	.1
Pacemaker	3.85 (1.06–14.0)	.04†	4.26 (1.15–15.8)	.03†
Chronic obstructive pulmonary disease	2.62 (0.82–8.34)	.1	2.11 (0.64–6.93)	.2
LV ejection fraction	0.61 (0.39–0.94)	.03†	0.60 (0.38–0.94)	.03†
LV E/e'	1.89 (1.16–3.08)	.01†	1.72 (1.03–2.87)	.04†
Mean right atrial pressure	2.13 (1.26–3.61)	.005†	1.91 (1.07–3.43)	.03†
RV end-diastolic pressure	1.87 (1.15–3.03)	.01†	1.59 (0.91–2.77)	.1
Mean pulmonary artery pressure	1.72 (1.04–2.83)	.03†		
Pulmonary vascular resistance	2.34 (1.28–4.29)	.006†	2.65 (1.08–6.49)	.03†
≥Moderate tricuspid regurgitation	2.00 (0.81–4.96)	.1	1.73 (0.68–4.39)	.3
RA reservoir strain	0.33 (0.17–0.63)	.001†	0.35 (0.18–0.68)	.002†
RA emptying fraction	0.35 (0.19–0.62)	<.001†	0.37 (0.20–0.67)	.001†
RA compliance	0.40 (0.19–0.85)	.02†	0.41 (0.19–0.91)	.03†

AF, atrial fibrillation; CI, confidence interval; LV, left ventricular; OR, odds ratio; RA, right atrial.

*Each parameter was adjusted for mean pulmonary artery pressure (PAP). Odds ratios for continuous variables represent an SD change.

† $P < .05$.

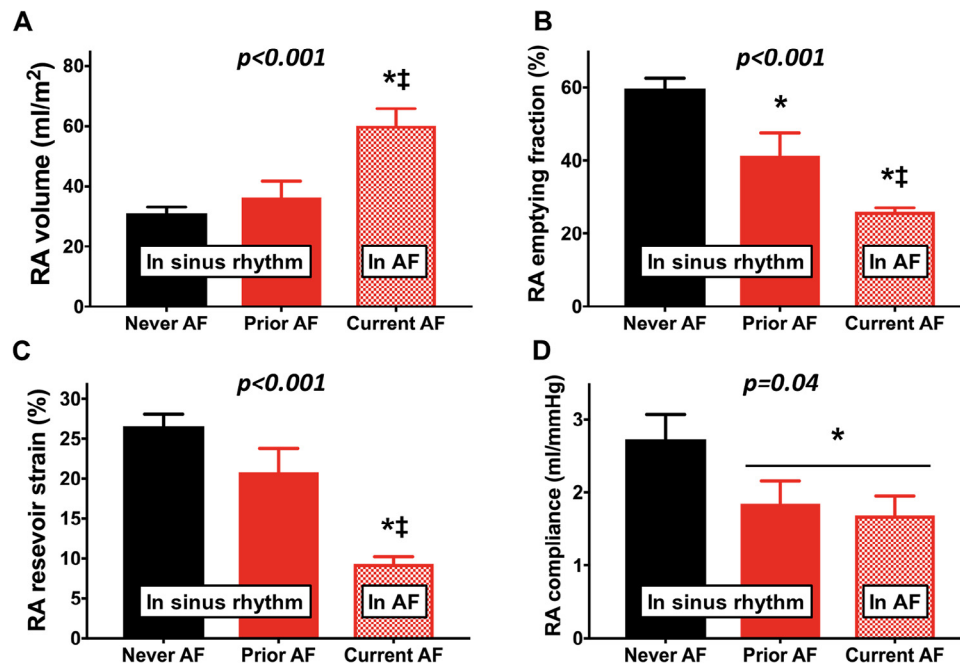


Fig. 3. Association between atrial fibrillation (AF) and right atrial (RA) function. $*P < .05$ vs Never AF group (with Bonferroni correction). $\ddagger P < .05$ vs Prior AF group (with Bonferroni correction). Error bars indicate SEM.

Right Atrial Function in Atrial Fibrillation Versus Sinus Rhythm

RA reservoir strain could be measured in 70 patients (76.9%), RA volume and emptying fraction in 72 (80.0%), and RA compliance in 56 (61.5%). As seen in Fig. 3, RA emptying fraction (16.2% vs 28.5%; $P < .001$) and RA reservoir strain (9.5% vs 24.3%; $P < .001$) were lower in AF than in sinus rhythm. RA volume index (62.7 vs 32.2 mL/m²; $P < .001$) was higher in AF than in sinus rhythm. For several RA parameters, there was a significant difference observed across the 3 subgroups. RA volume index increased across these subgroups (Fig. 3A), and RA emptying fraction and RA reservoir strain significantly decreased (Fig. 3B and C). Patients with earlier AF who were currently in sinus rhythm had significant lower RA emptying fraction than sinus rhythm patients without history of AF (41% vs 60%; $P = .002$). Patients with any diagnosis of AF had lower RA compliance than patients without any history of AF ($P < .001$; Fig. 3D).

The logistic regression models for the association with RA emptying fraction and reservoir strain below their medians are depicted in Table 3. Median RA emptying fraction was 42% (IQR 24 to 65%) and median reservoir strain was 18% (IQR 9%–28%). Atrial fibrillation and RV dysfunction were the strongest determinants of reduced RA emptying fraction and RA reservoir strain. In the patients in sinus rhythm, earlier AF was also significantly associated with lower reservoir strain compared with patients without any history of AF, even after adjustment for RVEDP (Table 3).

Discussion

The present study demonstrates that in patients with HFpEF, RV and RA function are more depressed in patients with AF than in patients in sinus rhythm. This association was independent from afterload. Moreover, patients in sinus rhythm during the assessment but who had earlier AF also displayed more RV and RA dysfunction than patients without any history of AF. Furthermore, reduced RA function was strongly and independently related to RV dysfunction in HFpEF.

The observation that RV dysfunction is more prevalent in patients with HFpEF who are in AF seems robust, because RV function was assessed with the use of multiple parameters and all of them pointed in the same direction. The present study therefore confirms and extends previous reports regarding the association between AF and RV dysfunction in HFpEF.^{4-7,9} In addition, the simultaneous availability of right heart catheterization and echocardiography in the present study, including RA functional parameters, as well as the identification of a 3rd subgroup consisting of patients in sinus rhythm but with earlier AF, are novel and add to the current data of right heart performance in HFpEF-AF. Besides AF, reduced LVEF, LV diastolic dysfunction, and pacing were also independently associated with RV dysfunction, similarly to previous observations.^{4,5,9}

Right Ventricular Function in Atrial Fibrillation Versus Sinus Rhythm

In general, RV dysfunction in HFpEF is strongly related to increased pulmonary pressures.¹⁷ In the present study,

Table 3. Correlates of Right Atrial Dysfunction

Variable	↓ RA Emptying Fraction		↓ RA Reservoir Strain	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Unadjusted model*				
Any diagnosis of AF vs Never AF	17.33 (5.15–58.3)	<.001 [‡]	14.50 (4.55–46.2)	<.001 [‡]
Earlier AF vs Never AF	3.86 (0.95–15.7)	.06	4.46 (1.05–19.0)	.04 [‡]
LA volume index	2.94 (1.37–6.30)	.006 [‡]	4.31 (1.75–10.64)	.002 [‡]
LA reservoir strain	0.20 (0.07–0.54)	.002 [‡]	0.16 (0.05–0.53)	.003 [‡]
Mean right atrial pressure	3.75 (1.74–8.06)	.001 [‡]	3.30 (1.60–6.79)	.001 [‡]
Mean pulmonary artery pressure	2.18 (1.20–3.99)	.01 [‡]	1.91 (1.07–3.40)	.03 [‡]
Pulmonary vascular resistance	3.06 (1.37–6.85)	.007 [‡]	1.57 (0.87–2.83)	.1
RV end-diastolic pressure	1.75 (1.02–3.00)	.04 [‡]	1.85 (1.07–3.20)	.03 [‡]
RV dysfunction	8.46 (2.78–25.8)	<.001 [‡]	8.20 (2.68–24.9)	<.001 [‡]
≥Moderate tricuspid regurgitation	3.12 (1.07–8.99)	.04 [‡]	1.30 (0.47–3.59)	.6
RVEDP-adjusted model [†]				
Any diagnosis of AF vs Never AF	13.28 (4.11–43.0)	<.001 [‡]	16.35 (4.72–56.7)	<.001 [‡]
Earlier AF vs Never AF	3.86 (0.95–15.7)	.06	4.57 (1.05–19.9)	.04 [‡]
LA volume index	2.94 (1.35–6.41)	.006 [‡]	4.81 (1.77–13.1)	.002 [‡]
LA reservoir strain	0.21 (0.07–0.60)	.003 [‡]	0.17 (0.05–0.58)	.005 [‡]
RV dysfunction	7.50 (2.42–23.2)	<.001 [‡]	7.12 (2.29–22.2)	.001 [‡]
≥Moderate tricuspid regurgitation	3.18 (1.07–9.51)	.04 [‡]	1.25 (0.44–3.57)	.7

LA, left atrial; RV, right ventricular; other abbreviations as in Table 2.

*Only significant associations with RA dysfunction are depicted in the table.

[†]Each parameter was adjusted for RV end-diastolic pressure (RVEDP). Odds ratios for continuous variables represent an SD change.

[‡] $P < .05$.

patients with AF had higher PCWP and PAP than patients in sinus rhythm. Both AF and RV dysfunction may therefore relate to worsening HFpEF with increasing LV filling pressures, leading on the one hand to LA hypertension, stretch, fibrosis, and subsequently AF,¹⁸ and on the other hand further backward to pulmonary hypertension (PH) and RV dysfunction. However, the association between AF and RV dysfunction was independent from RV afterload, which is in line with 2 previous studies.^{4,9} It was suggested that AF may directly contribute to RV dysfunction via impaired longitudinal performance, because it was demonstrated that cardioversion from AF to sinus rhythm was associated with an improvement of RV longitudinal contraction.¹⁹ This is supported by our finding that patients who were in AF had lower RV systolic tissue velocities than patients without any history of AF. However, the present observations of reduced RV function in patients with AF may also be caused by uncertainties of the measure itself in the setting of AF. For example, LVEF is generally underestimated and mitral regurgitation often overestimated with AF.¹² Furthermore, heart rate irregularity may also negatively affect biventricular function in heart failure,²⁰ and a similar phenomenon occurs with permanent pacing in HFpEF.^{5,9}

In contrast, RV dysfunction was also more prevalent in HFpEF patients with an earlier diagnosis of AF while currently in sinus rhythm compared with patients without any history of AF. In addition, the patients with earlier AF also displayed more RA remodeling than patients without a history of AF. To our knowledge, these findings—in HFpEF patients who were all in sinus rhythm—are novel and suggest that also factors other than heart rhythm play a role in the development of right-side remodeling in patients with HFpEF and AF. For example, impaired RA function and loss of “atrial kick” limits Frank-Starling recruitment,

which may further impair myocardial performance and might explain the close relation between RA remodeling and reduced RV function. Furthermore, the progression of AF is often an indication of worsening HFpEF.²¹ We therefore hypothesize that these observations might also be an expression of the development of right-side perturbations, simultaneously with left-side remodeling in the course of the disease, as similarly described by Borlaug et al recently in another HFpEF cohort.²²

Right Atrial Function in Atrial Fibrillation Versus Sinus Rhythm

HFpEF patients with AF had higher RA volumes and lower RA function and compliance. Interestingly, RA strain, emptying fraction, and compliance were also lower in HFpEF patients with earlier AF who were in sinus rhythm during the assessment. There are several potential explanations for these findings.

Although there are some distinct differences in anatomy between both atria,²³ AF and longstanding atrial dyssynchrony and stress in the setting of AF leads to structural remodeling changes in both atria simultaneously.²⁴ Furthermore, systemic inflammation and endothelial dysfunction driven by predominant comorbidities with HFpEF, such as renal dysfunction, diabetes mellitus, and obesity, target both atria equally and may facilitate atrial remodeling and AF.²⁵ In patients with paroxysmal AF, early signs of HFpEF with increased LA pressures at rest or during exercise are already prevalent and clinically relevant.²⁶ The left atrium serves as a buffer between the LV and pulmonary circulation, prohibiting transmission of left-side filling pressures to the pulmonary circulation. LA remodeling in HFpEF was therefore previously linked to increased LA pressure and PVR and elevated RV afterload.¹⁰

Thus, loss of compliance and buffering capacity of the LA in HFpEF-AF might result in enhanced backward transmission of left-side pressures and may trigger RV and RA remodeling.

In contrast, RA enlargement, stretch, and fibrosis in the setting of HFpEF-PH may perhaps also contribute to an RA-predominant substrate for AF, because we observed that RV and RA atrial pressures were much higher in patients with AF, compared with patients without AF diagnosis, than LVEDP and PCWP in AF versus no AF. In a retrospective cohort of 239 patients with PH, primarily with idiopathic pulmonary arterial hypertension and chronic thromboembolic PH, the prevalence of AF was 20% and the presence of AF was associated with higher PVR and PAP.²⁷ In another cohort, 58% of patients with PH due to left heart failure had AF, but AF was also present in 23% of patients with PH without left heart failure.²⁸ The latter group of patients also had more RA dilation and higher RA pressures than PH patients without left heart failure and without AF.²⁸ Furthermore, the onset of supraventricular tachyarrhythmias in pulmonary arterial hypertension might be a sign of further deterioration of right-side cardiac function.²⁹ The findings in the present study suggest that in some patients with HFpEF with high pulmonary pressures, AF might be triggered by RA overload rather than LA overload. Clearly, the present study cannot comment further on this hypothesis in the setting of HFpEF, owing to its cross-sectional design, but perhaps in future studies—with continuous monitoring of pulmonary pressures³⁰—elevation of right-side pressures can be linked to incident AF in patients with HFpEF.

Study Limitations

This was a small observational cohort study that has inevitable limitations. First, patients with earlier echocardiography-suspected PH were referred for right heart catheterization, resulting in a selection bias. Second, although the duration of AF diagnosis was known, it was unknown how long the patients with earlier AF were currently in sinus rhythm. RA function may still be impaired in sinus rhythm but with a very recent conversion, compared with patients who had much earlier conversion from AF to sinus rhythm before the assessment. In addition, although the echocardiographic assessments were performed with the use of multiple heart beats, AF can cause uncertainty of the echocardiographic measurement itself, owing to variation in cardiac filling and load with irregular heart rate. However, this phenomenon is less applicable to patients with a history of AF who were in sinus rhythm during the assessment. Furthermore, the cross-sectional design of the study prohibits any conclusions regarding cause-effect relations between AF and RV dysfunction. Finally, because of the sample size, multivariable associations with adjustment for more than 3 parameters were not possible.

Conclusion

In patients with HFpEF, both RV and RA function were gradually more depressed in patients who were in AF, as well as in patients in sinus rhythm but who had earlier AF, than in patients without any history of AF. These findings were independent from pulmonary pressures and suggest simultaneous right-side remodeling in patients with HFpEF and AF.

References

1. Gorter TM, Hoendermis ES, van Veldhuisen DJ, Voors AA, Lam CS, Geelhoed B, et al. Right ventricular dysfunction in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *Eur J Heart Fail* 2016;18:1472–87.
2. Linssen GC, Rienstra M, Jaarsma T, Voors AA, van Gelder IC, Hillege HL, et al. Clinical and prognostic effects of atrial fibrillation in heart failure patients with reduced and preserved left ventricular ejection fraction. *Eur J Heart Fail* 2011;13:1111–20.
3. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ, et al. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity (CHARM) program. *J Am Coll Cardiol* 2006;47:1997–2004.
4. Melenovsky V, Hwang SJ, Lin G, Redfield MM, Borlaug BA. Right heart dysfunction in heart failure with preserved ejection fraction. *Eur Heart J* 2014;35:3452–62.
5. Mohammed SF, Hussain I, Abou Ezzeddine OF, Takahama H, Kwon SH, Forfia P, et al. Right ventricular function in heart failure with preserved ejection fraction: a community-based study. *Circulation* 2014;130:2310–20.
6. Ghio S, Guazzi M, Scardovi AB, Klersy C, Clemenza F, Carluccio E, et al. Different correlates but similar prognostic implications for right ventricular dysfunction in heart failure patients with reduced or preserved ejection fraction. *Eur J Heart Fail* 2016;19:873–9.
7. Aschauer S, Kammerlander AA, Zotter-Tufaro C, Ristl R, Pfaffenberger S, Bachmann A, et al. The right heart in heart failure with preserved ejection fraction: insights from cardiac magnetic resonance imaging and invasive haemodynamics. *Eur J Heart Fail* 2016;18:71–80.
8. Lam CS, Rienstra M, Tay WT, Liu LC, Hummel YM, van der Meer P, et al. Atrial fibrillation in heart failure with preserved ejection fraction: association with exercise capacity, left ventricular filling pressures, natriuretic peptides, and left atrial volume. *JACC Heart Fail* 2017;5:92–8.
9. Bosch L, Lam CSP, Gong L, Chan SP, Sim D, Yeo D, et al. Right ventricular dysfunction in left-sided heart failure with preserved versus reduced ejection fraction. *Eur J Heart Fail* 2017;doi:10.1002/ejhf.873. Epub ahead of print.
10. Melenovsky V, Hwang SJ, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. *Circ Heart Fail* 2015;8:295–303.
11. Hoendermis ES, Liu LC, Hummel YM, van der Meer P, de Boer RA, Berger RM, et al. Effects of sildenafil on invasive haemodynamics and exercise capacity in heart failure patients with preserved ejection fraction and pulmonary hypertension: a randomized controlled trial. *Eur Heart J* 2015;36:2565–73.
12. Lang RM, Badano LP, Mor-Avi V, Afzal J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;28:1–39. e14.
13. Hussain I, Mohammed SF, Forfia PR, Lewis GD, Borlaug BA, Gallup DS, et al. Impaired right ventricular-pulmonary arterial coupling and effect of sildenafil in heart failure with preserved ejection fraction: an ancillary analysis from the Phosphodiesterase-5 Inhibition to Improve

- Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX) trial. *Circ Heart Fail* 2016;9:e002729.
14. Ko YG, Ha JW, Chung N, Shim WH, Kang SM, Rim SJ, et al. Effects of left atrial compliance on left atrial pressure in pure mitral stenosis. *Catheter Cardiovasc Interv* 2001;52:328–33.
 15. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. *J Clin Epidemiol* 1995;48:1503–10.
 16. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol* 1996;49:1373–9.
 17. Chatterjee NA, Steiner J, Lewis GD. It is time to look at heart failure with preserved ejection fraction from the right side. *Circulation* 2014;130:2272–7.
 18. Kotecha D, Lam CSP, van Veldhuisen DJ, van Gelder IC, Voors AA, Rienstra M. Heart failure with preserved ejection fraction and atrial fibrillation. vicious twins. *J Am Coll Cardiol* 2016;68:2217–28.
 19. Alam M, Samad BA, Hedman A, Frick M, Nordlander R. Cardioversion of atrial fibrillation and its effect on right ventricular function as assessed by tricuspid annular motion. *Am J Cardiol* 1999;84:1256–8. A8.
 20. Melenovsky V, Hay I, Fetis BJ, Borlaug BA, Kramer A, Pastore JM, et al. Functional impact of rate irregularity in patients with heart failure and atrial fibrillation receiving cardiac resynchronization therapy. *Eur Heart J* 2005;26:705–11.
 21. Brouwers FP, de Boer RA, van der Harst P, Voors AA, Gansevoort RT, Bakker SJ, et al. Incidence and epidemiology of new onset heart failure with preserved vs reduced ejection fraction in a community-based cohort: 11-year follow-up of PREVEND. *Eur Heart J* 2013;34:1424–31.
 22. Borlaug BA, Kane GC, Melenovsky V, Olson TP. Abnormal right ventricular-pulmonary artery coupling with exercise in heart failure with preserved ejection fraction. *Eur Heart J* 2016;37:3293–302.
 23. Ho SY, Sanchez-Quintana D. The importance of atrial structure and fibers. *Clin Anat* 2009;22:52–63.
 24. Platonov PG, Mitrofanova LB, Orshanskaya V, Ho SY. Structural abnormalities in atrial walls are associated with presence and persistency of atrial fibrillation but not with age. *J Am Coll Cardiol* 2011;58:2225–32.
 25. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol* 2013;62:263–71.
 26. Meluzin J, Starek Z, Kulik T, Jez J, Lehar F, Wolf J, et al. Prevalence and predictors of early heart failure with preserved ejection fraction in patients with paroxysmal atrial fibrillation. *J Card Fail* 2017;23:558–62.
 27. Olsson KM, Nickel NP, Tongers J, Hoepfer MM. Atrial flutter and fibrillation in patients with pulmonary hypertension. *Int J Cardiol* 2013;167:2300–5.
 28. Rottlaender D, Motloch LJ, Schmidt D, Reda S, Larbig R, Wolny M, et al. Clinical impact of atrial fibrillation in patients with pulmonary hypertension. *PLoS ONE* 2012;7:e33902.
 29. Rajdev A, Garan H, Biviano A. Arrhythmias in pulmonary arterial hypertension. *Prog Cardiovasc Dis* 2012;55:180–6.
 30. Gorter TM, Rienstra M, van Veldhuisen DJ. Measuring pulmonary artery pressures in heart failure: a new useful diagnostic tool? *Circulation* 2017;135:1518–21.